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CONTENTS

Organophosphate poisoning and management, an update

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Abstract

Organophosphate poisoning is characterised for the most part, by acute incidents. Management is by way of first aid (in mild poisoning) and use of atropine with or without the oximes, (in moderate to severe poisoning). Of late, it has become apparent that subchronic and chronic organophosphate poisoning are a common manifestation. This review paper summarises this triphasic nature of organophosphate poisoning. Possible future diagnostic and management techniques are also discussed.

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Introduction

Poisoning from pesticides accounts for 15% of all poisoning admissions cases in Zimbabwe, 10% of which are due to organophosphate (OP), pesticides.[1] Most OP poisoning incidents are associated with occupational exposures (in the agro-chemical industry), accidental poisonings (in industry/factory), and suicide/parasuicides. The bulk of pesticides used in Zimbabwe (over 50%) are organophosphates, (OPs).

Review

Organophosphate poisoning can be subdivided into three phases, i.e. acute poisoning, which is characterised by inhibition of nerve tissue acetylcholinesterase and accumulation of free unbound acetylcholine at the nerve endings of all cholinergic nerves; an intermediate syndrome, which consists of neurological signs, 24 to 96 hours after acute exposure; and an Organophosphate Induced Delayed Peripheral Neuropathy, (OPIDPN), which occurs seven to 14 days after exposure. Currently, there are a number of clinical research studies, aimed at enhancing management and definitive diagnosis of organophosphate poisoning.

Acute Poisoning.

Acute OP poisoning syndrome is characterised by inhibition of nerve tissue acetylcholinesterase and accumulation of free unbound acetylcholine at the nerve endings of all cholinergic nerves. The result is a continual stimulation of electrical activity. The signs and symptoms of acute OP poisoning can be subdivided into three categories, according to the severity of the poisoning.

Mild Poisoning: In mild poisoning, the victim can walk but may experience fatigue, headaches, dizziness, nausea and vomiting, numbness, sweating and salivation, tightness in the chest, abdominal cramps and diarrhoea. If the serum cholinesterase levels are inhibited by 20 to 50% of normal levels, it is recommended that atropine be administered (sulphate) i.v. or i.m. 1 to 2 mg every 10 to 15 minutes until signs of atropinization appear, i.e. dry mouth, dilated or normal pupils and pulse rate of between 75 to 85 per minute. The atropine dose should be repeated to maintain atropinization. If less than 24 hours have elapsed since the incident, pralidoxime, i.v. or i.m. may be given in addition. Under these conditions, the prognosis is usually good.[2,3]

Moderate Poisoning: In moderate poisoning the victim may have difficulty in walking or might not be able to walk at all. The serum cholinesterase activity is inhibited by over 80%. It is recommended that atropine be administered 1 to 2 mg every 10 to 15 minutes until atropinization. Atropinization should be maintained. If it is less than 24 hours since the exposure, pralidoxime, 1g i.v. or i.m. may be given and repeated every four to six hours. It is important to note that while oximes may be beneficial, Pralidoxime is associated with less side effects than Obidoxime, which in high doses is associated with hepatotoxicity. The rationale of using oximes is based on the fact that, if administered, within 24 hours, oximes, help to reverse the OP + cholinesterase interaction compound and thereby make available more enzyme.

By the point of atropinezation, some patients may experience and exhibit delirium and hallucinations, which is associated with atropine toxicity on the central nervous system.

Severe Poisoning: In severe poisoning, the patient may be unconscious and showing signs of difficulty in breathing. Other signs and symptoms are pupillary reflex to light, flaccid paralysis and prominent miosis. Because of the difficulty in breathing, the victim may be cyanotic. The serum cholinesterase activity levels are usually at least 95% inhibited. Treatment should consist of a high dose of atropine, 2mg i.v. every 10 minutes until sweating and/ or salivation disappear and /or mydriasis or normal pupil reaction develops. If not treated promptly, severe OP poisoning is fatal. Mechanical ventilation is needed in moderate to severe poisoning. Diazepam 10mg i.v., may be needed for convulsions and the dose may be repeated. Atropine eye drops may relieve headaches.[8]

Both plasma cholinesterase (sometimes referred to as pseudocholinesterase) and erythrocyte acetylcholinesterase are used for diagnosis of the magnitude of OP poisoning and monitoring of OP exposures. At the same intensity of exposure, plasma cholinesterase is significantly more inhibited than erythrocyte cholinesterase. Plasma cholinesterase recovery to normal (pre-exposure) levels takes 50 days and that of erythrocyte cholinesterase recovers after 82 days (interestingly a time frame that is shorter than the life-span of erythrocytes). As a result, the recommended minimum period without exposure, to establish pre-exposure base-line levels is 60 days.[9] However, it must be pointed out that most diagnoses of acute organophosphate poisoning are made clinically and this is reliable.

Intermediate Poisoning.

The intermediate syndrome (IMS) of organophosphate poisoning consists of neurological signs 24 to 96 hours after acute toxic exposure. These signs are characterised by muscle weakness, (muscles innervated by the cranial nerves i.e. the neck, flexors and respiratory muscles) and the limbs. This may be accompanied by respiratory depression and distress. Urgent ventilation of the victim may be required. Some of the organophosphates that are associated with the intermediate syndrome are fenithion, dimethoate, monocrotophos and methamidophos. There is no known antidote for this syndrome.

Chronic Poisoning.

Some organophosphates induce delayed neurotoxicity, referred to as Organophosphate Induced Delayed Peripheral Neuropathy, (OPIDPN).[10]

OPIDPN is characterised pathologically, by symmetrical sensory motor axonopathy which tends to be severe in long axons. The histological lesion is a "dying back" of axons as opposed to demyelination. Clinically the syndrome is associated with flaccid paralysis of the lower limbs and in severe cases the upper limbs too. There is muscle weakness

in arms and legs leading to clumsy shuffling and high stepping gait. This may be replaced by spasticity and abnormal reflexes, perhaps a pointer to damage to the pyramidal tracts.[11]

OPIDPN occurs seven to 14 days after exposure. There is no known treatment for it. Recovery in victims is limited to the arms and legs but foot drops, spasticity and hyperactive reflexes may become irreversible. It is suggested that this is a result of spinal cord injury.

The Future.

Some of the OP[1] which are associated with OPIDPN include, EPN (on-ethyl o-p-nitrophenyl phenylphosphonate), cyanofenphos and trichloronat. These OPs inhibit a non specific carboxylesterase called the neuropathic target estarase (NTE). A 70 to 80% inhibition of NTE results in induction of OPIDPN. The OPs with potent anticholinesterase activity have no OPIDPN activity at all.

Current clinical research in organophosphate poisoning is aimed at optimising both treatment and definitive diagnosis. Promising results have come out of research using erythrocytes as carrier models of phosphotriesterase to antagonize the toxic effects of OPs. Erythrocytes, packed with a recombinant phosphotriesterase have been shown to provide protection against toxicity to paraoxon, an OP. Phosphotriesterase hydrolyses paraoxon to a non toxic metabolite,[12] and this would augument the use of atropine.

As far as definitive diagnosis is concerned, the recent development of a sensitive ELISA (enzyme-linked immunosorbent assay) for the measurement of protein mass of serum cholinesterase (CHE) provides exciting promises. It is envisaged (and has been demonstrated in clinical research on OP poisoned patients) that protein mass determination of serum CHE provides valuable information concerning the target value of serum CHE activity for treatment of OP poisoning patients. The technique is also valuable for investigating the specific activity of generic variants of serum CHE.[13]

Both the intermediate and chronic syndromes seem to be related to the chemical nature of the compound and may also be a result of ineffective management of the acute syndrome.

Conclusion

In conclusion, it has been established that OP poisoning has three phases, as outlined above. Recent developments have pointed at improved development of diagnostic methods and management of diagnostic and management techniques.

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